



## **A Framework for Optimization of Bioprocess Operation under Uncertainties: A lignocellulosic Ethanol Production Case Study**

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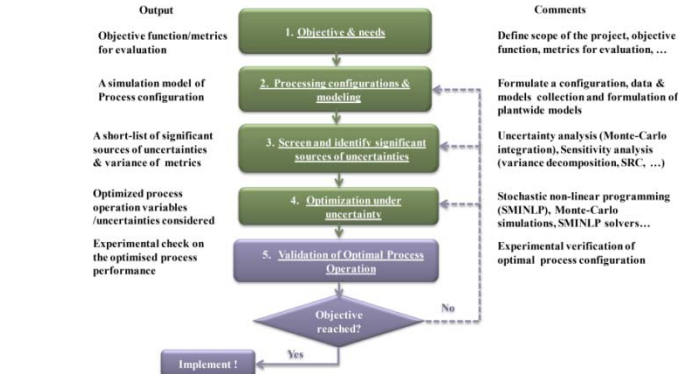
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## I. Introduction

This study presents the development and application of a systematic model-based framework for bioprocess optimization. The framework relies on the identification of sources of uncertainties via global sensitivity analysis, followed by the quantification of their impact on performance evaluation metrics via uncertainty analysis. Finally, stochastic programming is applied to drive the process development efforts forward subject to these uncertainties.

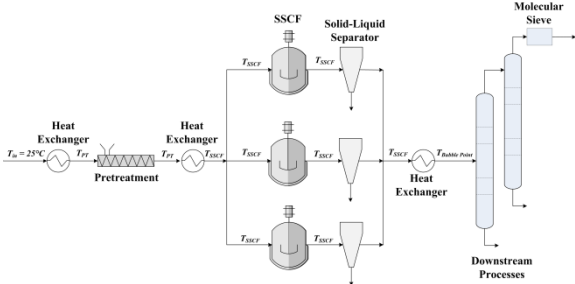
## III. A Framework for Bioprocess Optimization under Uncertainty



## II. Objective:

To develop a *framework* to solve the *optimization problem of bioprocesses subject to uncertainties* in particular *identify the significant sources of uncertainties* and *optimize production cost of lignocellulosic ethanol*

## IV. Case Study: Lignocellulosic Ethanol Production



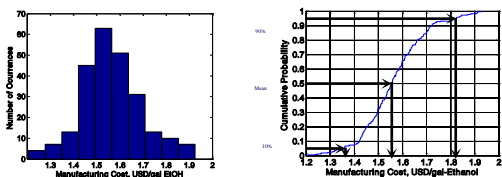
Simultaneous Saccharification and Co-Fermentation operating in continuous.

(Morales-Rodriguez, et al., 2011, *Bioprocess Technol.* (102) 1174-1184.)

## V. Screen and Identify Significant Sources of Uncertainty

The uncertainty analysis is carried out using the Monte-Carlo technique. The sensitivity analysis is done by Morris screening.

### Uncertainty Analysis



Variance: measure of uncertainty  
 $\sigma^2 = 0.017$  ( $\sigma = 0.13$ )

### Sensitivity Analysis

$$EE_{\mu} = \frac{\partial y_{\mu}}{\partial \theta_j} = \frac{y_{\mu}(\theta_1, \theta_2, \theta_3 + \Delta, \dots, \theta_M) - y_{\mu}(\theta_1, \theta_2, \theta_3, \dots, \theta_M)}{\Delta}$$

Morris method relies on *estimating the distribution of the elementary effects (EE) of each input parameter (j) on the  $k^{\text{th}}$  model output  $EE_{\mu}$*

	Ethanol yield $\mu$	Std. Dev.	SEM		Operating Cost $\mu$	Std. Dev.	SEM
$C_{\text{FE}}$	0.63	0.26	0.07	$C_{\text{UT}}$	-0.44	0.32	0.08
$C_{\text{FE}}$	-0.20	0.09	0.02	$C_{\text{FE}}$	0.16	0.12	0.03
$C_{\text{FE}}$	-0.22	0.10	0.03	$C_{\text{FE}}$	0.14	0.10	0.02
$C_{\text{FE}}$	-0.06	0.05	0.01	$E_{\text{Eth}}$	0.29	0.68	0.18
$C_{\text{FE}}$	-0.16	0.16	0.04	$E_{\text{Eth}}$	0.42	0.41	0.11
$E_{\text{Eth}}$	-0.28	0.55	0.14	$\alpha$	-0.11	0.06	0.02
$E_{\text{Eth}}$	0.17	0.44	0.11	$k_{\text{FE}}$	-0.03	0.15	0.04
$\alpha$	0.10	0.05	0.01	$V_{\text{max,G}}$	0.08	0.22	0.06
$V_{\text{max,G}}$	-0.09	0.25	0.06	$Y_{\text{Eth,G}}$	-0.13	0.16	0.04
$Y_{\text{Eth,G}}$	0.09	0.18	0.05	$E_{\text{Eth,G}}$	-0.28	0.22	0.06
$E_{\text{Eth,G}}$	0.23	0.19	0.05	$E_{\text{Eth,G}}$	-0.07	0.12	0.03
$E_{\text{Eth,G}}$	0.06	0.10	0.03				

Sin et al. (2009), *Biotechnology Progress*, 25, 1043-1053

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## VI. Optimization under Uncertainty

Formulation of the optimization problem under uncertainty (Stochastic NLP)

$$\begin{aligned} \min_x & \{ Z(x) = c^T x + E[f(x, \theta)] \} \\ \text{s.t.} & \\ & h(\theta) = 0 \\ & g(\theta) \leq 0 \\ & \theta^{\text{LB}} \leq \theta \leq \theta^{\text{UB}} \end{aligned}$$

Obj is to minimize unit production Cost

$$\min_x Z(x, \theta) = c_{\text{FE}} \text{Feedstock}(\theta) + c_{\text{UT}} \text{Utilities}(x, \theta) + c_{\text{ADD}} \text{Additives}(x, \theta)$$

$$c_{\text{FE}} \text{Ethanol}(x, \theta) = \frac{\text{USD}}{\text{gal Ethanol}}$$

$c_{\text{FE}}$  = selling cost per kg of ethanol,  $c_{\text{FE}}$  = unit cost of consumed feedstock,  $c_{\text{UT}}$  = unit cost of consumed utilities,  $c_{\text{ADD}}$  = unit cost of consumed additives

Uncertainty:  
Sampling from high-dimensional operation space  
Sampling of uncertain parameter space  
For  $i=1$ : Number of Operation Scenarios  
For  $j=1$ : Number of uncertain future scenarios  
 $\text{Obj}1(j) = \text{Objective function}(\theta_{\text{eta}})$   
s.t.  $F(\theta_{\text{eta}})$  & inequality & equality c.s.  
End  
 $\text{Obj}2 = \text{mean}(\text{Obj}1)$   
End

### Raw optimization results under uncertainty (SNLP)

Scenario ID	Manufacturing cost, USD/gal				Relative change wrt	
	95% CI	mean	95% CI	variance $\sigma^2$	% change (95% CI)	% change saving (mean) (95% CI)
Base case	1.36	1.56	1.82	0.017	-	-
67	1.27	1.48	1.66	0.012	6.33	5.30 8.67
45	1.31	1.47	1.69	0.013	3.45	6.23 6.87
40	1.28	1.48	1.70	0.015	6.06	5.15 6.25
87	1.38	1.57	1.75	0.012	-1.42	-0.39 3.55
70	1.42	1.58	1.79	0.015	-4.09	-1.28 1.41
80	1.39	1.56	1.79	0.016	-2.10	0.47 1.39
7	1.36	1.57	1.81	0.020	-0.31	-0.10 0.23

### Optimal operation scenario / (values of continuous variables)

	$C_{\text{Acid}}$ % (wt/v)	$T_{\text{PT}}$ °C	$T_{\text{SCF}}$ °C	$EL_1$ mg-Enz/g-cellulose	$EL_2$ g/L	$C_{\text{FE}}$ g/L	% $\text{EtOH}$	Mean manufacturing cost USD/gal-EtOH
Base case	1.1	170	35	40	40	9.5	0.5	1.56
Optimal	0.78	142	33	31	34	13.6	0.46	1.48
UB	0.55	140	17.5	20	20	4.7	0.4	-
LB	1.65	175	35	60	60	14.2	0.6	-

## VII. Other Process Configurations

Configurations	5% CI	mean	95% CI	% saving (5% CI)	% saving (mean)	% saving (95% CI)
Base case (SSCF)	1.36	1.56	1.82	-	-	-
SSCF C-RECY	1.13	1.29	1.43	-16.91%	-17.31%	-21.43%
SHCF double recycle	1.36	1.54	1.71	-0.21%	-1.26%	-6.27%
SHCF single recycle	1.62	1.74	1.87	18.85%	11.47%	2.51%

\* Savings in relation to based case scenario

### Relative improvements in consumption of additives

Configuration	Additives	% change wrt base case
SSCF-C	Acid Loading	-29
SSCF-C-RECY	Enzyme Loading	-39
SHCF with double recycle	Enzyme Loading	-26
SHCF with single recycle	Enzyme Loading	-2

## VI. Discussion and Concluding Remarks

- A model-based framework for bioprocess optimization under uncertainties: identify them, quantify them, optimize under them & iterate
- The most significant sources of uncertainties affecting unit production cost of ethanol: (i) feedstock composition, (ii) degree of hydrolysis of cellulose and (iii) ethanol yield on glucose and xylose. These uncertainties leads to an uncertainty of 0.26 USD/gal-eth in unit production cost.
- With stochastic optimisation, operation ideas generated to bring down the production costs further (up to 21%),
- The framework is generic and can be applied to analyze the impact of market as well as political uncertainties (e.g. subsidies) on bioprocess development efforts.

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